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Secondary somatosensory cortex evoked responses and 6-year neurodevelopmental outcome in extremely preterm children

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HIGHLIGHTS

- Unilaterally absent secondary somatosensory cortex (SII) responses at term age predicted worse motor outcome at 6 years.
- SII responses were equally present in 6-year-old preterm and term-born children.
- Motor inhibition affected SII responses differently in preterm and term-born children.

ABSTRACT

Objective: We assessed in extremely preterm born (EPB) children whether secondary somatosensory cortex (SII) responses recorded with magnetoencephalography (MEG) at term-equivalent age (TEA) correlate with neurodevelopmental outcome at age 6 years. Secondly, we assessed whether SII responses differ between 6-year-old EPB and term-born (TB) children.
Methods: 39 EPB children underwent MEG with tactile stimulation at TEA. At age 6 years, 32 EPB and 26 TB children underwent MEG including a sensorimotor task requiring attention and motor inhibition. SII responses to tactile stimulation were modeled with equivalent current dipoles. Neurological outcome, motor competence, and general cognitive ability were prospectively evaluated at age 6 years.
Results: Unilaterally absent SII response at TEA was associated with abnormal motor competence in 6-year-old EPB children (p = 0.03). At age 6 years, SII responses were bilaterally detectable in most EPB (88%) and TB (92%) children (group comparison, p = 0.69). Motor inhibition was associated with decreased SII peak latencies in TB children, but EPB children lacked this effect (p = 0.02).
Conclusions: Unilateral absence of an SII response at TEA predicted poorer motor outcome in EPB children.
Significance: Neurophysiological methods may provide new means for outcome prognostication in EPB children.

1. Introduction

An estimated 15 million babies were born preterm globally in 2014 and approximately 4% of them were born extremely preterm, i.e., before 28 weeks of gestation (Chawanpaiboon et al., 2019). Extremely preterm birth may result in an encephalopathy encompassing lesions in the periventricular areas, cerebral white matter, thalamus, basal ganglia, cerebral cortex, brainstem, and/or cerebellum (Volpe, 2009). Subsequently, a substantial proportion of extremely preterm born (EPB) children grow up with neurodevelopmental impairment (Myrhaug et al., 2019). Com-

Abbreviations: CI, confidence interval; EPB, extremely preterm born; ECD, equivalent current dipole; GOF, goodness-of-fit; IQR, inter-quartile range; ISI, interstimulus interval; IVH, intraventricular hemorrhage; MEG, magnetoencephalography; MND, minor neurological dysfunction; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; PMA, postmenstrual age; SD, standard deviation; SEP, somatosensory evoked potential; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; SIIc, contralateral secondary somatosensory cortex; SIIi, ipsilateral secondary somatosensory cortex; TB, term-born; TEA, term-equivalent age; US, ultrasound; WMI, white matter injury.

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pared with their term-born (TB) peers, EPB children show significantly more frequently motor (Bolk et al., 2018; Spittle et al., 2018) and cognitive deficits (Joseph et al., 2016; O'Reilly et al., 2020), especially in executive functions including e.g. attention and inhibition (Joseph et al., 2016).

Early identification of the extremely preterm born infants who are at the greatest risk for subsequent adverse neurodevelopment is fundamental. Different brain imaging and neurophysiological techniques are currently employed to predict the preterm-born infants' risk for future adverse outcome, e.g., early and late cerebral ultrasound (US), term-equivalent magnetic resonance imaging (MRI) (Woodward et al., 2006; Hintz et al., 2015; Hintz et al., 2018), electroencephalography (Hellström-Westas and Rosen, 2005), and somatosensory evoked potentials (SEP) (Pierrat et al., 1997; Pike and Marlow, 2000). However, even serial neuroimaging (Hintz et al., 2018) or the combination of all the above-mentioned methods (Franckx et al., 2018) have shown limited prospective diagnostic validity, which has raised interest in finding additional methods for outcome prediction and to understand the underlying pathophysiology.

Regarding the sensorimotor system, somatosensory processing beyond afferent pathways and the primary somatosensory cortex (SI) can be detected with magnetoencephalography (MEG) (Hari and Forss, 1999). The secondary somatosensory cortex (SII) is of particular interest as it is thought to be involved in higher-order somatosensory processing, e.g., bimanual integration (Jung et al., 2012) and tactile object recognition (Reed et al., 2004). Furthermore, in adults, SII response amplitudes correlate with scores from hand-function tests at the acute phase of a stroke and during recovery from it (Forss et al., 2012). In a cohort of EPB infants, absent SII responses to tactile stimulation in MEG at term-equivalent age (TEA) have been significantly more prevalent than in TB infants (Nevalainen et al., 2015) and predicted worse neurodevelopmental outcomes at two years of corrected age (Rahkonen et al., 2013; Nevalainen et al., 2015). The EPB children from the same cohort have also shown reduced reactivity of certain neural oscillations in sensorimotor areas during a motor response inhibition task in MEG at age 6 years (Pihko et al., 2017) and worse sensorimotor performance at age 7 years (Lönnberg et al., 2018) than their TB controls. There is, however, no information available about how the neonatal MEG findings transfer to MEG findings in later childhood and the children's performance.

We set out to study whether the absent SII responses previously discovered at TEA were a long-lasting characteristic of these EPB children and whether the neonatal MEG findings would still be correlated with neurodevelopmental outcome in 6-year-old EPB children. Secondly, we assessed the effect of a sensorimotor Go/NoGo task on the SII responses at age 6 years in an effort to further understand the mechanisms underlying attention- and inhibition-related problems prevalent in the EPB children. As studies on somatosensory evoked responses in children have mostly focused on the early responses on SI, and studies on SII responses in children are very limited (Nevalainen et al., 2014; Saby et al., 2016), we also describe the characteristics of SII responses in 6-year-old children. We hypothesized that: 1) absent SII responses at TEA would predict worse neuromotor outcome in 6-year-old EPB children, 2) SII responses would be absent in 6-year-old EPB children more often than in TB children, and 3) motor inhibition and attention to the stimuli would affect the SII responses more clearly in 6-year-old TB than EPB children.

2. Methods

2.1. Participants

The participants were originally recruited for a larger multimethodological study (KeKeKe Study—Extremely Preterm Birth and Development of the Central Nervous System, Rahkonen et al., 2013; Nevalainen et al., 2015; Pihko et al., 2017; Lönnberg et al., 2018) where EPB children (gestational age < 28 completed weeks) and their TB controls (gestational age 37 to 42 completed weeks) have been prospectively followed up since birth. The EPB children, born in 2006–2008, were treated at the neonatal intensive care unit of the Helsinki University Hospital in Finland. The TB children were born healthy in 2006–2009 in the Hospital District of Helsinki and Uusimaa.

39 EPB children of the cohort attended MEG at TEA. One child was excluded from the current analyses due to a later diagnosed chromosomal abnormality and two children lacked all data on neurodevelopmental outcome at age 6 years (see Fig. 1 for the inclusion and exclusion of the children). The remaining 36 children's data were used to study the correlation between SII responses at TEA and neurodevelopmental outcome at age 6 years. Table 1 presents clinical characteristics of these 36 EPB children included in the analysis.

From the original cohort, we further enrolled 32 EPB (of which 18 attended MEG also at TEA) and 26 TB children to attend a MEG recording at age 6 years, but we subsequently excluded one TB child from the analysis due to technical problems in the recording. Children who were suspected not to be able to co-operate sufficiently in the MEG recording, which is, per se, demanding given the young age of our participants, were not invited to attend MEG (see Fig. 1 for the inclusion and exclusion of the children). Table 1 presents clinical characteristics of the 57 children included in the MEG analysis at age 6 years.

2.2. Ethical considerations

The local ethics committee of the Hospital District of Helsinki and Uusimaa granted ethical approval for the study. The parents or caregivers of all the participating children signed an informed consent in accordance with the Declaration of Helsinki. All the participating 6-year-old children gave consent to participate after receiving age-appropriate information about the study.

2.3. Clinical data and magnetic resonance imaging

Obstetric and neonatal data were collected from the hospital records and by a parental questionnaire. The EPB infants underwent brain MRI at TEA for the assessment of the degree of white matter injury (WMI) which was classified to either none, mild, moderate, or severe (Woodward et al., 2006).

High-resolution T1-weighted brain MRI scans, used as anatomical references for the MEG responses, were available from 12 EPB and 14 TB children at the mean (SD) age of 7.6 (0.1) years (EPB vs. TB, p = 0.34). The MRI scanning took place at the Advanced Magnetic Imaging Centre of Aalto University, Helsinki, Finland with a 3-tesla MAGNETOM Skyra scanner (Siemens Healthcare, Erlangen, Germany). Anatomical landmarks (nasion, left and right preauricular points) were identified from the images for the use of the MEG-MRI-integration.

2.4. MEG recordings at term-equivalent age

39 EPB infants of the KeKeKe cohort participated in a MEG recording at TEA. Infants needing respiratory support or constant monitoring at TEA could not participate. The protocol of the recordings has been reported in detail elsewhere (Nevalainen et al., 2015). The infants were asleep during the recording with no sedation. The MEG device was the same Vectorview device as used for the MEG recordings at age 6 years (see Ch. 2.5 MEG recordings at age 6 years). The infants lay on their side with one hemisphere over the occipital part of the dewar helmet and data

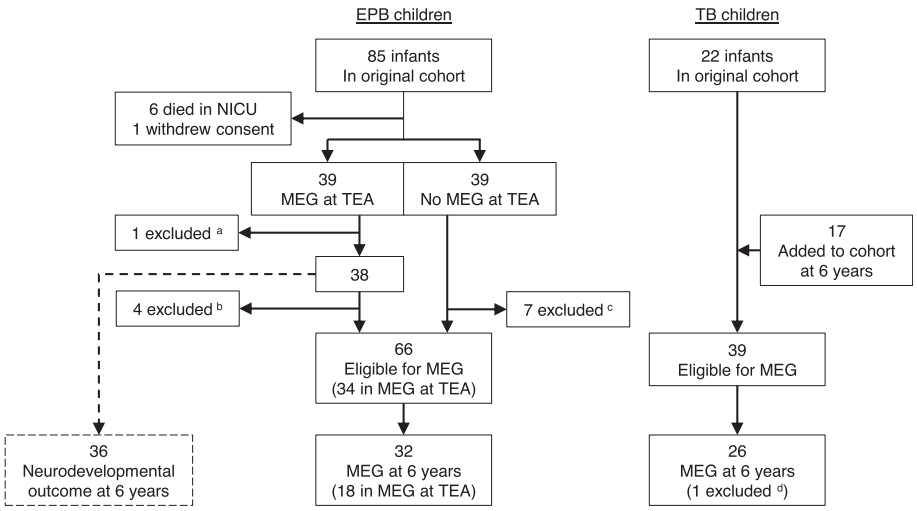

Fig. 1. Flow chart of the inclusion of children to the study. Excluded due to: [a] chromosomal abnormality, [b] cognitive impairment (2), insufficient native language skills (1), mutism (1), [c] cognitive impairment (6), insufficient native language skills (1), and [d] technical problems in MEG recording. EPB, extremely preterm born; MEG, magnetoencephalography; NICU, neonatal intensive care unit; TB, term-born; TEA, term-equivalent age.

Table 1
Characteristics of the participants.

Characteristic		EPB children in MEG at TEA with neurodevelopmental outcome at age 6 years (n = 36)	EPB children in MEG at age 6 years (n = 32)	TB children in MEG at age 6 years[a] (n = 25)
General demographics				
	Males	20 (56%)	20 (63%)	13 (52%)
	PMA/age in MEG recording, mean (SD)	41.4 (1.4) weeks	6.5 (0.1) years	6.5 (0.1) years
	Right-handed [b]	.	26 (81%)	22 (88%)
Neonatal demographics				
	Gestational age at birth (wk), median (IQR)	26.6 (1.7)	26.4 (1.8)	40.3 (1.2)**
	Birth weight (g), mean (SD)	878 (187)	840 (165)	3670 (390)**
	Small for gestational age[c]	4 (11%)	6 (19%)	0 (0%)*
	Twins	9 (25%)	8 (25%)	0 (0%)*
Neonatal morbidity				
	Bronchopulmonary dysplasia at h 36 + 0 [d]	15 (42%)	17 (59%)	.
	Necrotizing enterocolitis	2 (6%)	0 (0%)	.
	Retinopathy of prematurity[d]	6 (17%)	9 (29%)	.
Brain imaging in NICU IVH in neonatal ultrasound				
	No	23 (64%)	20 (62.5%)	.
	Grade I–II	7 (19%)	7 (21.9%)	.
	Grade III–IV	6 (17%)	5 (15.6%)	.
White matter injury in MRI at TEA[d]				
	No	25 (73.5%)	20 (67%)	.
	Mild	8 (23.5%)	7 (23%)	.
	Moderate	1 (3%)	3 (10%)	.
	Severe	0 (0%)	0 (0%)	.

Data are n (%) unless otherwise specified.
EPB, extremely preterm born; IQR, interquartile range; IVH, intraventricular hemorrhage; MEG, magnetoencephalography; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; PMA, postmenstrual age; SD, standard deviation; TB, term-born; TEA, term-equivalent age.
[a] Comparison of the participating EPB and TB children: $^{*}p < 0.5$, $^{**}p < 0.001$
[b] According to writing hand at age 6 years.
[c] Birth weight less than −2 SD according to Finnish growth references.
[d] Data not available for all EPB children in MEG at age 6 years as follows: Bronchopulmonary dysplasia (3), Retinopathy of prematurity (1) and White matter injury in MRI at TEA (2, and 2 EPB children in MEG at TEA with neurodevelopmental outcome at age 6 years).

from only one hemisphere was collected at a time. The tactile stimulus was given to the index finger of the right and left hands in separate runs. Data from both hemispheres to both contra- and ipsilateral stimuli were collected and SI and SII responses were modeled with equivalent current dipoles (ECD). The SII response was perceived as absent when neither contra- nor ipsilateral stimuli evoked an SII response on the hemisphere (left or right).

2.5. MEG recordings at age 6 years

MEG was recorded in a magnetically shielded room in the BioMag Laboratory, Helsinki, Finland with a sensor array consisting of 306 independent channels (102 identical sensor triplets with two orthogonally-oriented planar gradiometers and one magnetometer) covering the whole head (Elekta Neuromag Vectorview or, in

11 TB children's measurements, TRIUX, Elekta Oy, Helsinki, Finland). We applied continuous head position measurement during the recording using data from the position indicator coils attached to the child's head and other anatomical landmarks (i.e., nasion, left and right preauricular points) and scalp shape digitized before the recording. Electro-oculography was recorded simultaneously with MEG. The MEG recording settings and procedure used are described in more detail here (Pihko et al., 2017).

The child lay supine with his/her head supported by thin cushions in the measurement helmet and was instructed to lie still and look at a picture on the ceiling to prevent excessive eye-movements (Fig. 2). Compliance to the given tasks was ensured by a researcher present in the measurement room giving instructions. One parent was also allowed to join in. The whole MEG recording session lasted approximately 45 min and the child was given an opportunity to move his/her limbs during small breaks between recording blocks that lasted less than 10 min each.

2.5.1. Tactile stimulus

During the MEG recording, the index and little finger were stimulated with a tactile stimulus. The tactile stimuli, gentle taps to the fingertip, were provided by an inflatable plastic diaphragm expanded by pulses of compressed air (Somatosensory Stimulus Generator, 4-D NeuroImaging Inc., San Diego, CA, USA) in a semi-random sequence (60% index finger and 40% little finger). The inter-stimulus interval (ISI) between consecutive stimuli was 2 s and one recording block included altogether at least 250 stimuli.

2.5.2. Measurement conditions: NO-TASK and TASK

In this study, we used data from two recording conditions using the tactile stimulus described above. Since handedness has not been reported to affect the SII response amplitudes (Simões et al., 2002; Zhu et al., 2007; Jung et al., 2009), to study the effect of the NO-TASK vs. TASK conditions, we used the same side of stimulation for all subjects irrespective of handedness (see Table 1).

In the NO-TASK condition, the children were asked to relax and listen to a story, and to ignore the tactile stimuli. The TASK condition included a Go/NoGo task where the child was instructed to attend to the given stimuli and squeeze a soft, non-magnetic toy with the opposite, right, hand each time he/she felt the stimulus on the left little finger (Go), and not to squeeze when he/she felt the stimulus on the left index finger (NoGo). The correctness of the physical response (squeeze / no squeeze) was estimated by muscular activity from four electromyography skin electrodes placed on the volar side of the right hand and forearm.

Two EPB children and one TB child discontinued the measurement session before the TASK condition recording and, therefore, only data from the NO-TASK condition are used for these children. Also, data from the NO-TASK condition from one EPB child were excluded due to excessive head movement during the measurement.

2.6. MEG data analysis at age 6 years

The collected MEG data from each recording block were visually inspected and channels with artifacts or excessive sensor noise were discarded. The MEG data were then preprocessed with the spatiotemporal signal space separation method (Taulu and Simola, 2006) of the Maxfilter® software (Elekta Neuromag®; Elekta Oy, Helsinki, Finland) to suppress external magnetic artifacts as well as to apply continuous head movement compensation (time window 16 s and correlation limit 0.98).

Only data from the index finger stimulation, with no motor responses, were used in the analyses. Preprocessed data for index finger stimulation were averaged time-locked to stimulus (each epoch from −100 ms to 500 ms), baseline corrected (100 ms pre-stimulus) and low-pass filtered at 90 Hz. We discarded from the

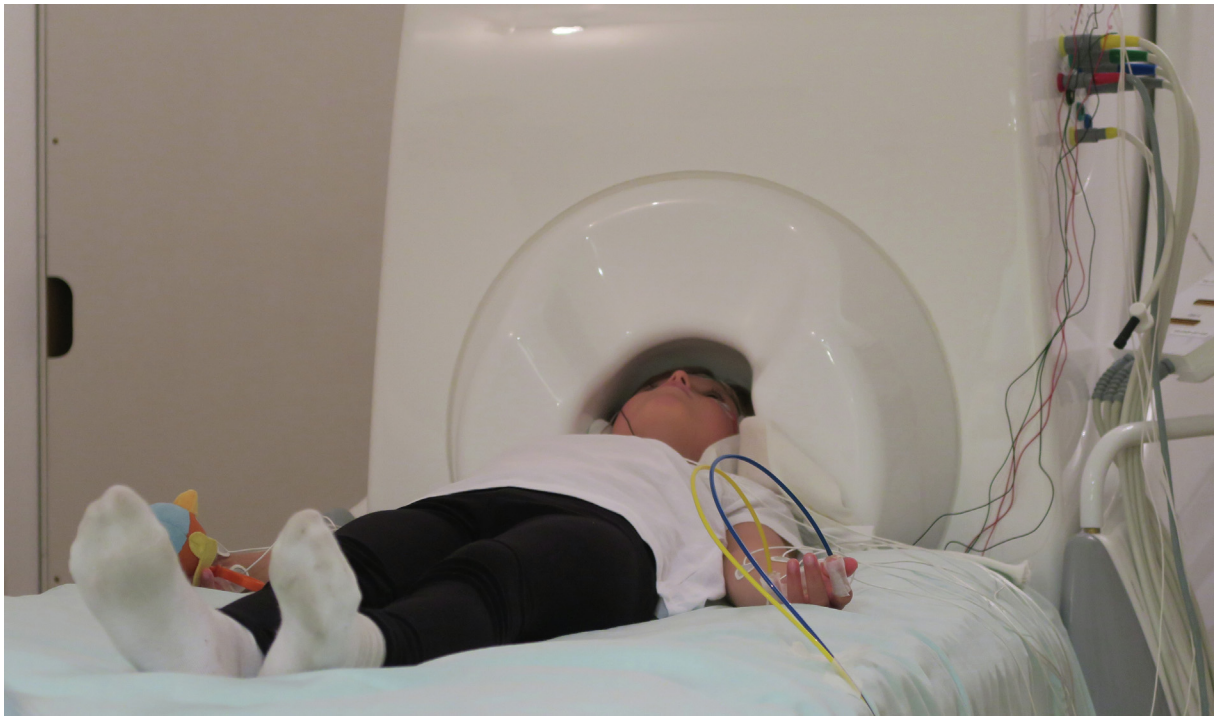

Fig. 2. A magnetoencephalography recording during the TASK condition. The subject is lying still on the bed with the subject's head in the dewar helmet. The thin plastic tubes (blue and yellow) are connected to the Somatosensory Stimulus Generator outside the magnetically shielded room and drive air pulses to plastic diaphragms gently fastened with skin tape to the subject's left index and little finger. The subject is holding a soft nonmagnetic toy in the right hand in order to respond to the tactile stimuli the subject feels on the little finger. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

averages epochs containing MEG activity over 3000 fT/cm on the gradiometer channels, or over 8000 fT on the magnetometer channels. For each child, we identified recording blocks where excessive eye movements could distort the data by visually comparing averaged data sets with and without rejections for electro-oculographic activity over 150 mV in the XPlotter® software (Elekta Neuromag®, Elekta Oy, Helsinki, Finland). Consequently, in one child, we constructed signal space projection vectors for electro-oculography traces and projected them out of the data, instead of discarding his/her data. For the TASK condition, we also discarded epochs with clear electromyographic activity to suppress the effect of the motor activity of the incorrect squeezes to the somatosensory evoked magnetic fields. As reported in our previous paper (Pihko et al., 2017) on a subgroup (22 EPB children without major brain abnormalities and 21 TB children) of all the children attending MEG, judging by the electromyography traces, EPB children gave significantly fewer correct responses to both Go- and NoGo-stimuli than TB children (79% vs. 89% and 71% vs. 86%, respectively) and, additionally, had significantly more difficulty in the NoGo inhibition task than in the Go task ($p = 0.01$). There were, however, no significant differences between the number of the averaged epochs for EPB and TB children in either NO-TASK or TASK condition in the current analyses [median (IQR) in NO-TASK: EPB 164 (9), TB 161 (23), $p = 0.13$; and TASK: EPB 131 (30), TB 138 (28), $p = 0.30$].

2.6.1. Equivalent current dipole modeling

We applied ECD modeling with XFit® software (Elekta Neuromag®; Elekta Oy, Helsinki, Finland) to estimate the location, strength and orientation of the current source in the primary somatosensory cortex (SI) contralateral to stimulus and the secondary somatosensory cortex both contra- (SIIc) and ipsilateral (SIIi) to stimulus. We used a spherical head model fitted to the Isotrak data and visually selected 10–25 channel triplets with prominent activity over the area of interest to estimate the source location. We first fitted single dipoles for the first prominent SI response from the individually selected MEG channels, with 1-ms intervals around the visually determined peak corresponding to the previously described M50 response (Pihko et al., 2009). Thereafter, if the SI ECD distorted the SII ECD modeling, its activity was subtracted from the data before modeling the SII response in the same way as the SI response. We selected the ECDs (one for SI and one for each SII) with the greatest dipole moment, presuming a dipolar magnetic field pattern and goodness-of-fit (GOF) over 75% (mean 90.8%, SD 5.3%) to be used in the multi-dipole model. For subjects with MRIs at age 7 years, the location of the ECD was reviewed from the MR images with the MEG-MRI integration software (Elekta Neuromag®; Elekta Oy, Helsinki, Finland) and for others from a standard 3-D head model. Subsequently, we calculated a time-varying multi-dipole model, where both SI and SII dipoles are simultaneously active and their strengths and directions of current flow are allowed to vary with time while the locations and orientations are kept constant. In case we were not able to get an acceptable fit for SIIc and/or SIIi, we used the mean location and orientation from the accepted ECD fits to construct the multi-dipole model (no significant difference between EPB and TB children in the use of this method). We calculated these mean ECD parameters separately for EPB and TB children, in the NO-TASK and TASK condition and for SIIc and SIIi, separately (acceptable fits: EPB NO-TASK SIIc n = 17, SIIi n = 14, TASK SIIc n = 13, SIIi n = 11; TB NO-TASK SIIc n = 15, SIIi n = 17, TASK SIIc n = 15, SIIi n = 13). SII ECDs' location coordinates or orientation vectors did not differ more than 3 SD from the mean in any subject. The average locations of the accepted ECDs are presented in Supplementary Table 1.

We determined the strength and latency of the SI and SII responses from the multi-dipole model at the peak of each response (posteriorly pointing dipole for SI and anteriosuperiorly pointing dipole for SII). These values were then used in further statistical analyses. A response was considered present when there was a visually recognizable peak in the source waveform (between 30 ms and 100 ms for SI, and between 100 and 300 ms for SII) and a dipolar magnetic field pattern with orientation and location compatible with those of SI or SII sources. When these criteria were not met, the strength of the ECD was set at zero and peak latency as a missing value. When an acceptable SIIc and/or SIIi response was present in neither NO-TASK nor TASK condition, the child was considered to lack the response.

To be able to assess the possible absence of the SII responses at age 6 years in a similar manner as in MEG at TEA (see chapter 2.4 MEG recordings at term-equivalent age), we also recorded one block while stimulating the right hand in the same way as the left hand described above (see chapter 2.5.1 Tactile stimulus). The data on the right index finger's stimulation were processed and modeled similarly as data on the left hand's stimulation but were only used for the detection of the SII responses if they were absent from the recordings with the left hand's stimulation.

2.7. Neurodevelopmental outcome measures for 6-year-old EPB children

Neurological outcome was assessed with a neurological examination according to Touwen (Touwen, 1979; Hadders-Algra, 2010) at the median (IQR) age of 6.6 (0.4) years. The assessment consists of eight domains including posture and muscle tone, reflexes, involuntary movements, coordination and balance, fine manipulation, associated movements, sensory system, and cranial nerve function. The outcome is categorized as optimal, minor neurological dysfunction (MND) 1, MND 2 or cerebral palsy, where optimal and MND 1 (non-optimal) are considered as normal and MND 2 and cerebral palsy as abnormal outcomes.

Motor competence was assessed with the Second Edition of the Movement Assessment Battery for Children, MABC 2, (Henderson et al., 2007) at the median (IQR) age of 6.7 (0.3) years. The assessment consists of eight items covering manual dexterity, balance and ball skills. Total or any subtest score at or under the 16th percentile or diagnosed cerebral palsy were considered as abnormal motor competence.

General cognitive ability was determined by full-scale intelligence quotient which was assessed by performing five subtests (Block Design, Matrix Reasoning, Picture Completion, Information, and Vocabulary) of the Finnish edition of the Wechsler Preschool and Primary Scale of Intelligence, Third Edition, WPPSI-III (Wechsler, 2009) at the median (IQR) age of 6.5 (0.3) years. A full-scale intelligence quotient at or below 85 was considered as abnormal.

The EPB children with bilaterally present SII responses at TEA were studied for general cognitive ability at a slightly younger median age (IQR) [6.5 (0.3) years] than the EPB children with unilaterally absent SII response at TEA [6.7 (0.3) years, $p = 0.04$]. Otherwise, there was no significant difference in the assessment age for the neurodevelopmental outcome measures between these two groups of EPB children.

2.8. Statistics

Statistical analyses were performed with SPSS version 25 (IBM SPSS Statistics, IBM Corporation, US). Comparisons between groups of children (i.e. EPB and TB children, EPB subgroups according to MEG results at TEA, or participant and dropout EPB children) were performed with Student's t-test, Mann Whitney U, χ^2 or Fisher's

exact test depending on the nature and normality of data. Shapiro-Wilk test p-value < 0.05 determined non-normal distribution of continuous variables. Mantel-Haenszel Chi-square test was used for group comparisons on neonatal brain imaging (US and MRI) due to their ordinal nature. Neurodevelopmental outcomes between EPB subgroups according to the result of the MEG recording at TEA were compared with Logistic regression. Comparisons between different measurement conditions (NO-TASK and TASK) and different hemispheres (SIIc and SIIi) were performed with repeated measures statistical tests. ANOVA was used to study SII response peak latencies. The normality of the test residual distribution was assessed visually from graphs to ensure the test assumptions were met. Pairwise comparisons for the factors with significant effect on the ANOVA were performed. Statistical significance, using two-tailed comparison, was set at 0.05.

3. Results

3.1. Representativeness of the study groups

The EPB children who participated in MEG at TEA and had 6-years' neurodevelopmental outcome data available (n = 36) did not differ significantly in gender, neonatal demographics, and morbidity (listed in Table 1), or the grade of intraventricular hemorrhage (IVH) in neonatal US from the other EPB survivors of the cohort (refer to flow-chart in Fig. 1, n = 41, p > 0.05, data not shown). The EPB participants, with MEG at TEA and neurodevelopmental outcome at age 6 years, had, however, more likely normal MRI findings at TEA as they expressed mild or moderate WMI less often than the EPB dropouts (24% vs. 34% and 3% vs. 14%, respectively, p = 0.04). There were no cases with severe WMI in MRI in this cohort, and none of the EPB children studied here had periventricular leukomalacia in neonatal US.

The EPB children enrolled for the MEG recording at age 6 years (n = 32) did not differ significantly from the other EPB children eligible for the study (n = 34) in gender, neonatal demographics and morbidity, or brain imaging during neonatal treatment listed in Table 1 (p > 0.05, data for non-participants not shown). The EPB and TB children who attended MEG recording at age 6 years differed from each other by neonatal demographics but there was no significant difference in gender, age in MEG recording, or handedness (see Table 1 for details).

3.2. Presence of MEG responses and their relation to outcome measures

3.2.1. MEG at TEA and neurodevelopmental outcome at age 6 years

SI responses were present in all EPB children at TEA. Ten EPB children showed a unilaterally absent SII response at TEA, seven from the right hemisphere and three from the left hemisphere, and this group had significantly higher odds for abnormal motor competence at age 6 years than EPB children who had bilateral SII responses at TEA (n = 22) (see statistics in Table 2). There was, however, no significant difference in neurological or cognitive outcome between these groups. In addition, there were four EPB children with bilaterally absent SII responses at TEA and each of them had altogether normal neurodevelopmental outcomes at age 6 years. The sensitivity of the unilaterally absent SII response at TEA as a predictor for abnormal motor competence at age 6 years was 54% and specificity 94% with a positive predictive value of 88% and a negative predictive value of 73%.

Since motor competence was associated with MEG findings at TEA, we studied further how they were associated with neuroimaging findings in the neonatal period. Fig. 3 shows the relationship between unilaterally absent SII response and findings in neonatal US and MRI with motor outcome at age 6 years. Of the 36 EPB children included, altogether 13 had abnormal motor competence and 6 (46%) of them were missed by both US and MRI. Four of those six children had, however, an abnormal finding in MEG at TEA, i.e., unilaterally absent SII response. In general, children with abnormal motor competence were mostly identified with MEG and US, but not very often by MRI. Due to the small number of children studied, however, we performed no statistical comparisons between the three methods, MEG, US, and MRI, on their predictive capabilities. The four children with a unilaterally absent SII in MEG and IVH in neonatal US had both abnormalities consistently in the same hemisphere (right).

3.2.2. Presence of SI and SII responses at age 6 years

At age 6 years, SI responses were detectable in all children. SII responses to left hand's stimulation were present in EPB children as often as in TB children with no significant difference between the groups (p = 0.79). The SIIc response was found in 28 (88%) EPB children (25 in the NO-TASK condition and three additional children in the TASK condition) and 22 (88%) TB children (21 in the NO-TASK condition and one additional child in the TASK condition). The SIIi response was found in 28 (88%) EPB children (24 in the NO-TASK condition and four additional children in the TASK condition) and 22 (88%) TB children (21 in the NO-TASK condition and one additional child in the TASK condition). Altogether 26 (81%) EPB and 21 (84%) TB children had SII responses present both contra- and ipsilaterally, 2 (6%) EPB children and 1 (4%) TB child only on the SIIc, 2 (6%) EPB children and 1 (4%) TB child only on the SIIi, and 2 (6%) EPB and 2 (8%) TB children on neither hemisphere. There was no significant difference in the number of data epochs averaged between the children in whom the SII responses were present and those who lacked the SII response on one or both hemispheres (p > 0.1).

For the six EPB and four TB children who did not show both SIIc and SIIi responses to the left hand's stimulation, we examined the MEG data on the right hand's stimulation to discover whether these children lacked the SII responses, uni- or bilaterally, in a similar manner as in MEG at TEA. After taking into account also the right hand's stimulation, SII responses were bilaterally present in altogether 28 (88%) EPB and 23 (92%) TB children (no difference between the groups, p = 0.69). One TB child showed SII responses on neither hemisphere, and SII response on the right hemisphere was absent in three EPB children and one TB child and on the left hemisphere in one EPB child.

3.2.3. MEG at TEA vs. MEG at age 6 years

Only three children with a unilaterally absent SII response at TEA underwent MEG also at age 6 years, and two of them now showed bilateral SII responses while one had an absent SII response on the right hemisphere at TEA as well as at age 6 years (Table 2). Also, we could not detect SII response on the left hemisphere at age 6 years in one EPB child who had bilateral SII responses at TEA. Three of the four EPB children with bilaterally absent SII responses at TEA underwent MEG at age 6 years and they all showed bilateral SII responses.

3.3. Characteristics of the MEG responses at age 6 years and the effect of TASK

The source waveforms and magnetic field patterns of typical SI, SIIc, and SIIi responses and their source locations at age 6 years are illustrated in Fig. 4, and the variation in source waveforms of the SII ECD sources in the whole study population in Fig. 5.

Table 2
Neurodevelopmental outcome and SII responses at age 6 years in extremely preterm born children with bilaterally present and unilaterally absent SII responses at term-equivalent age.

		Bilaterally present SII responses (N = 22)	Unilaterally absent SII response (N = 10)	OR (95% CI)	*p*
Neurological examination					
	Normal, n (%)	16 (76%)	7 (70%)	1.4 (0.3 – 7.4)	0.71
	Abnormal, n (%)	5 (24%)	3 (30%)		
	No data, n	1	0		
Motor competence					
	Normal, n (%)	12 (67%)	1 (12.5%)	14.0 (1.4 – 141)	0.025
	Abnormal, n (%)	6 (33%)	7 (87.5%)		
	No data, n	4	2		
General cognitive ability					
	Normal, n (%)	16 (80%)	7 (78%)	1.1 (0.2 – 7.8)	0.89
	Abnormal, n (%)	4 (20%)	2 (22%)		
	No data, n	2	1		
SII responses at age 6 years					
	Normal, n	11	2		
	Unilaterally absent, n	1	1		
	Bilaterally absent, n	0	0		
	No data, n	10	7		

In addition, four extremely preterm born children had bilaterally absent SII responses at term-equivalent age, each of them showing normal neurological, motor, and cognitive outcome. CI, confidence interval; OR, odds ratio; SII, secondary somatosensory cortex.

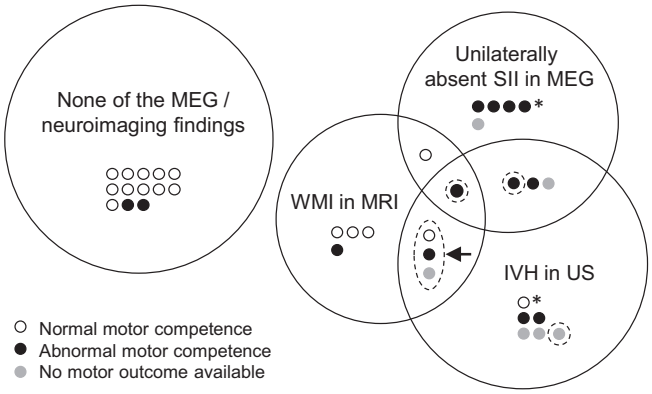

Fig. 3. Relationship between MEG at term-equivalent age and neonatal neuroimaging with motor competence at age 6 years in 36 EPB children. Each dot represents one EPB child and the color of the dot refers to the child's motor outcome at age 6 years. The big circles show which children had unilaterally absent SII in MEG and/or mild to moderate WMI in MRI at TEA and/or any grade of IVH in neonatal US. The dashed lines encircle the children with IVH grade III-IV and the arrow points out the only child with moderate WMI. The two children who did not have MRI at TEA are indicated with an asterisk. IVH, intraventricular hemorrhage; MEG, magnetoencephalography; MRI, magnetic resonance imaging; TEA, term-equivalent age; US, ultrasound; WMI, white matter injury.

3.3.1. Peak latency

The distributions of SI response peak latencies were skewed and, thus, we used nonparametric tests for comparisons between groups (EPB and TB) and conditions (NO-TASK and TASK). Peak latency for SI response in the NO-TASK condition [median (IQR) EPB: 40.5 (11.4) ms, TB: 40.8 (8.5) ms; $p = 0.77$] or in the TASK condition [EPB: 40.5 (11.4) ms, TB: 42.4 (7.3) ms; $p = 0.69$] showed no significant difference between the groups. There was no significant difference between the two conditions, NO-TASK and TASK, in either EPB or TB children's data ($p > 0.1$).

For the SII response peak latencies, we used repeated measures ANOVA to study the effect of *group* (EPB and TB), *hemisphere* (contralateral and ipsilateral to the stimulated hand) and *condition* (NO-TASK and TASK). Latency data for both SIIc and SIIi in both NO-TASK and TASK conditions were available from 13 EPB and 18 TB children who were, thus, included in this analysis. The effect of *group* was nonsignificant, but the effect of *hemisphere* [$F(1, 29) = 21.8$, $p < 0.001$] was significant with longer latencies on the ipsilateral than contralateral hemisphere [mean difference (95% confidence interval, CI) = 20.3 (11.4–29.2) ms] in both groups (interaction *hemisphere* × *group* ns.). There was also a significant effect of *condition* [$F(1, 29) = 10.0$, $p = 0.004$] with shorter latencies in the TASK than NO-TASK condition [mean difference (95% CI) = -13.1 (-21.5 to -4.6) ms]. The interaction *condition* × *group* was significant [$F(1, 29) = 5.6$, $p = 0.02$] showing that the difference in latencies between the conditions was due to a great decrease in latency in the TASK condition in TB children only (Fig. 6) best seen on the ipsilateral hemisphere but also present in the contralateral hemisphere (interaction *condition* × *group* × *hemisphere* ns.). The interpretations above were cross-checked with ANOVAs performed for EPB and TB children separately. In the analysis for EPB children only, there was a significant effect of *hemisphere* only ($p = 0.001$). In the analysis for TB children only, there was a significant effect of both *hemisphere* ($p = 0.01$) and *condition* ($p = 0.002$).

3.3.2. Source strength

The source strengths of neither SI nor SII responses were normally distributed and, hence, we analyzed them with nonparametric tests. There were no significant differences in the SI response source strengths between EPB and TB children or between the two conditions, NO-TASK and TASK (Table 3).

There were no significant differences in the SII response source strengths between the two groups of children, hemispheres, or measurement conditions (Table 3). These results did not change when we recalculated the individual source strengths as an average covering the response peak ± 10 ms around the maxima, counted with 1-ms intervals. As we were able to detect the SII responses in only one of the two conditions in some children and since there was no significant difference between the source strengths in different measurement conditions, comparison of the source strengths between EPB and TB children was also performed using only one source strength from either NO-TASK or TASK condition: the greater one. This did not change the results ($p > 0.4$). Comparison of source strengths between NO-TASK and TASK conditions, separately for EPB and TB children, was also performed by treating the source strengths of the not-detectable SII responses as missing values instead of with a value 0 (refer to Methods chapter 2.6.1 Equivalent current dipole modeling), and the results remained the same ($p > 0.3$).

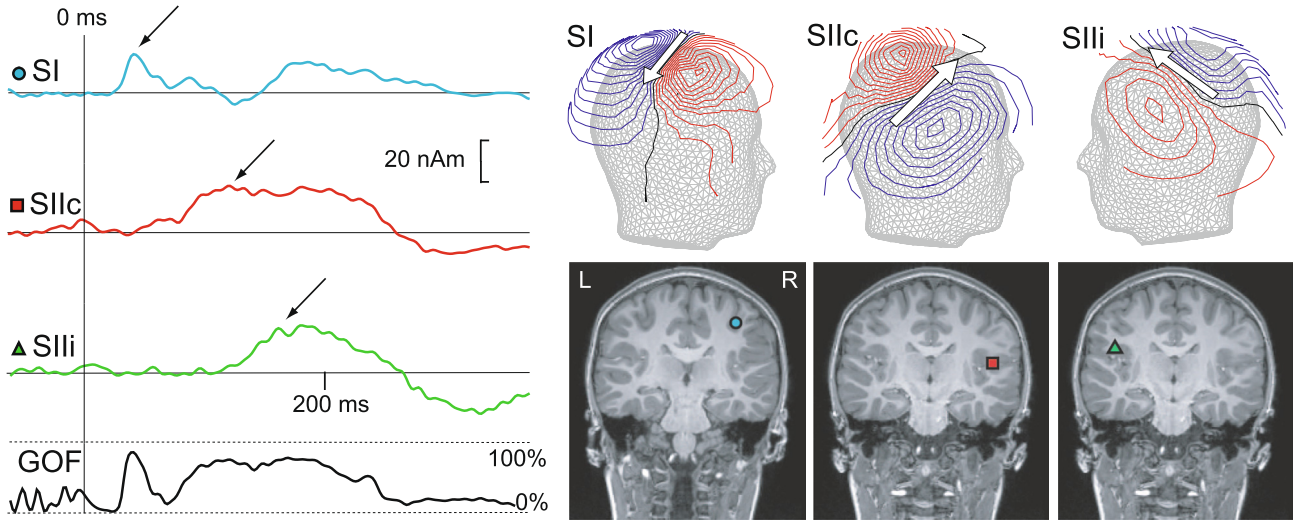

Fig. 4. SI, SIIc and SIIi responses in one representative 6-year-old term-born child. Left: Multidipole model showing the time courses of dipole moments (source waveforms in nAm) for SI, SIIc and SIIi responses. The three dipolar sources explain the data well as indicated by the goodness-of-fit (GOF) trace at the bottom. The vertical line indicates the time of the tactile stimulus to the left index finger. Right: Isofield contour maps reflected on the MEG helmet showing the magnetic field patterns of SI, SIIc and SIIi responses at timepoints reflected by black arrows on the source waveform image on the left. The contour step is 20 fT, the blue lines indicate the magnetic flux entering the head and the red lines the magnetic flux exiting the head. White arrows on the contour maps display the locations and orientations of the ECDs with lengths proportional to the ECD strength. The locations of the ECDs are also shown on coronal magnetic resonance images below each contour map image agreeing with the locations of the primary and secondary somatosensory cortices. ECD, equivalent current dipole; MEG, magnetoencephalography; SI, primary somatosensory cortex; SIIc, secondary somatosensory cortex contralateral-to-stimulus; SIIi, secondary somatosensory cortex ipsilateral-to-stimulus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

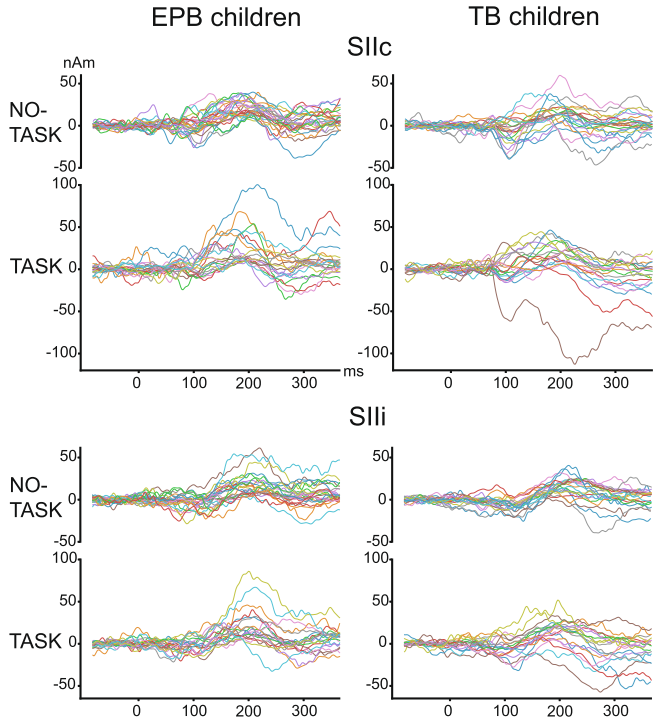

Fig. 5. Individual SII ECD source waveforms in the whole study groups of extremely preterm born (EPB) and term-born (TB) children at age 6 years. Time courses of dipole moments from the multi-dipole model showing source waveforms of all studied children with SIIc and/or SIIi responses present in the NO-TASK and TASK condition showing the trend and variation of the modeled SII responses within the study groups. Time point zero indicates the timing of the tactile stimulus. ECD, equivalent current dipole; SIIc, secondary somatosensory cortex contralateral-to-stimulus; SIIi, secondary somatosensory cortex ipsilateral-to-stimulus.

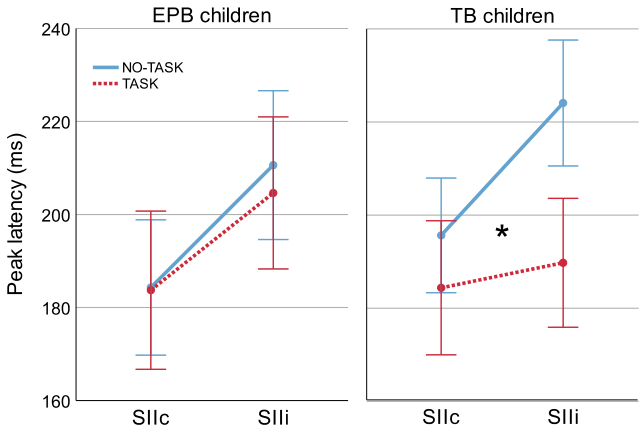

Fig. 6. Effect of TASK on SII response peak latency at age 6 years. Mean peak latencies of the SII responses in extremely preterm born (EPB) and term-born (TB) children on contra- (SIIc) and ipsilateral (SIIi) hemisphere to left hand's tactile stimulation in the NO-TASK (tactile stimulus while resting) and TASK condition (tactile stimulus while performing a task requiring attending to the stimuli and inhibiting a motor response). Whiskers indicate 95% confidence intervals of the means. The difference in the SII response peak latencies between TASK and NO-TASK conditions in the ANOVA was significant in TB children only (effect of condition p = 0.002, indicated with an asterisk in the figure). SII, secondary somatosensory cortex.

4. Discussion

We studied SII responses to tactile stimulation with MEG in EPB infants at TEA and in EPB and TB children at age 6 years. In accordance with our hypothesis, unilateral absence of an SII response at TEA was associated with abnormal motor competence at age 6 years in EPB children. Contrary to our hypothesis, however, there

Table 3
ECD source strengths (nAm) of the SI and SII responses with comparison between groups (EPB and TB children), measurement conditions (NO-TASK and TASK), and hemispheres (SIIc and SIIi).

		EPB	TB	EPB vs. TB (p)
SI				
	NO-TASK, median (IQR)	14.7 (12.2)	13.9 (10.6)	0.90
	TASK, median (IQR)	14.3 (15.7)	16.6 (13.3)	0.99
	NO-TASK vs. TASK (p)	0.46	0.12	
SIIc				
	NO-TASK, median (IQR)	18.8 (18.9)	14.5 (14.8)	0.11
	TASK, median (IQR)	13.9 (33.5)	15.1 (29.0)	0.99
	NO-TASK vs. TASK (p)	0.51	0.57	
SIIi				
	NO-TASK, median (IQR)	13.1 (18.5)	15.7 (18.2)	0.61
	TASK, median (IQR)	14.5 (26.1)	17.8 (24.9)	0.92
	NO-TASK vs. TASK (p)	0.90	0.96	
SIIc vs. SIIi (p)				
	NO-TASK	0.11	0.99	
	TASK	0.28	0.32	

ECD, equivalent current dipole; EPB, extremely preterm born children; IQR, interquartile range; SI, response on primary somatosensory cortex; SIIc, response on secondary somatosensory cortex contralateral-to-stimulus; SIIi, response on secondary somatosensory cortex ipsilateral-to-stimulus; TB, term-born children.

was no difference in the presence or absence of SII responses in 6-year-old EPB and TB children. Finally, motor inhibition affected SII response peak latencies in only TB but not EPB children.

4.1. SII responses at term-equivalent age and associations with outcome at age 6 years

In our EPB cohort, a unilaterally absent SII response at TEA was associated with abnormal motor competence at 6 years of age which is in line with our previous report of the same cohort at 2 years of corrected age, where absence of SII responses at TEA was associated with poorer mean developmental quotient and locomotor subscale in Griffiths Mental Developmental Scale assessment (Rahkonen et al., 2013). Surprisingly, bilaterally absent SII responses at TEA were associated with an altogether normal outcome at age 6 years which replicates the finding at 2 years of corrected age (Nevalainen et al., 2015). Hence, it seems that only interhemispheric asymmetry in SII responses, i.e., absence of an SII response unilaterally, represents an abnormal finding in MEG at TEA. Unilateral absence of an SII response has, by now, been reported only among EPB (Nevalainen et al., 2015) but not TB infants (Nevalainen et al., 2012). Interestingly, also newborn infants with prenatal exposure to buprenorphine showed an absent SII response more often (4/11 infants) than their non-exposed controls (1/11 infants) (Kivistö et al., 2015). Only one hemisphere of these infants was studied, however, and, consequently, no conclusion on the asymmetry of the SII responses can be made. Furthermore, the developmental outcome of these infants has not been reported.

Half of the EPB children with a unilaterally absent SII response at TEA had no IVH in US or WMI in MRI in the neonatal period, but still had abnormal motor competence at age 6 years. The presence of IVH in neonatal US was also usually associated with abnormal motor competence at age 6 years, but also missed many children with abnormal outcome. Comparison between different neuroimaging modalities and MEG on their ability to predict future outcomes would require a greater study cohort. Our results indicate, however, that neurophysiological methods detecting brain function can identify abnormalities that are not reflected on the commonly used structural imaging but are still associated with adverse outcome.

4.2. SII responses at age 6 years

Contrary to our hypothesis deriving from MEG recordings at TEA, where EPB infants had absent SII responses significantly more often than TB infants (Nevalainen et al., 2015), SII responses were equally present in 6-year-old EPB and TB children. Furthermore, two of the EPB children who showed unilateral absence of an SII response at TEA now had responses present bilaterally. This apparent discrepancy may reflect the different underlying mechanisms and significance of the SII response in neonates vs. adults or older children. During early development, neural activity plays a fundamental role in the refinement of functional connectivity, topographic maps, and higher-order associative circuits (Luhmann and Khazipov, 2018). During the preterm period, spontaneous movements and somatosensory stimuli evoke large oscillatory responses in the sensorimotor cortical areas (Leikos et al., 2020), which are thought to be the human equivalent of spindle bursts, which are critical for the development of the sensorimotor system in rodents (Luhmann and Khazipov, 2018). Although the somatosensory responses are no longer quite spindle burst -like in term neonates, the responses still have several immature properties (Lauronen et al., 2006; Nevalainen et al., 2008). For example, whereas in adults SII responses are enhanced by attention (Hamada et al., 2003) and diminish in stage N1 and N2 of non-rapid eye movement sleep (Kitamura et al., 1996; Kakigi et al., 2003) and are completely absent in slow wave sleep (our own unpublished observation), in neonates SII responses are detected particularly during quiet sleep (the neonatal equivalent of non-rapid eye movement sleep) (Nevalainen et al., 2008). This might indicate that the neonatal responses still mainly play a role in ontogeny rather than matured adult-like information processing. Hence, we suspect that the asymmetry in SII responses at TEA could have reflected an ontogenically disadvantageous functional brain state in that developmental phase rather than specific damage to the SII.

The SII responses develop with age. At age 6 years, the mean peak latencies in both EPB and TB children (approximately 180–220 ms) were considerably longer than latencies reported in adults (Hari et al., 1993; Hoechstetter et al., 2000; Wegner et al., 2000; Hadoush et al., 2010; Kida et al., 2018) but somewhat shorter than in neonates (Nevalainen et al., 2014) and in line with reports on school-aged children (Lauronen et al., 2002; Lin et al., 2003). There was a significant difference between the latencies for contra- and ipsilateral responses, both in EPB and TB children, as in previous adult studies (Hari et al., 1993; Wegner et al., 2000).

4.3. Effect of TASK on SII responses

The TASK condition affected the SII response peak latencies, but only in TB children. Similarly, one study in adults showed shorter

SIIc response peak latencies in the attending vs. ignoring condition when using a long ISI (5 s) (Hamada et al., 2003), but others showed no significant differences (Lam et al., 2001; Fujiwara et al., 2002). In our TB children, the TASK condition, which requires attending to the tactile stimuli and inhibiting a motor response, seemed to shorten the SII response peak latencies most clearly on the SII ipsilateral to the tactile stimulus which is, at the same time, contralateral to the inhibited motor response. The difference in SII response peak latencies could, thus, be a result of differences in cortical processing required for motor inhibition rather than attention to the tactile stimulation per se. The finding that TB children show such adjustability to the changing requirements of the response inhibition task, that EPB children are lacking, follows a similar pattern as our previous report on sensorimotor alpha oscillations (Pihko et al., 2017). Elevated alpha oscillation levels are suggested to reflect top-down inhibitory control (Klimesch et al., 2007). We previously found that, with the NoGo stimulus of the TASK condition, the alpha oscillations levels were enhanced over the sensorimotor cortex contralateral to the inhibited motor response, in a similar manner as reported in healthy adults (Nakata et al., 2013), in only TB, but not EPB children, (Pihko et al., 2017). In adults, significant SII response latency differences have, however, not been reported with a very similar Go/NoGo task (Nakata et al., 2005). As there are considerable differences in the SII response peak latencies between children and adults, this adjustability might show up in a different manner in our group of 6-year-olds compared with adults.

In contrast to the difference in latencies, we discovered no effect of the TASK condition on SII source strength. In adults, the SII responses are enhanced by attending to the somatosensory stimuli, which is usually implemented by silently counting either all (Hamada et al., 2003) or a specific type of the stimuli (Mima et al., 1998; Hoechstetter et al., 2000; Fujiwara et al., 2002). Attention to the tactile stimulus has also enlarged the activated areas on SII in functional MRI studies (Hämäläinen et al., 2000; Johansen-Berg et al., 2000). The lack of this effect in our study might stem from our subjects attending to the tactile stimuli on the little finger, which is non-adjacent to the index finger that was used in our analysis. In adults, SII responses are enhanced only when attention is drawn specifically to the site of the stimulus that evokes them, e.g., attending to only one of the two stimulated hands (Lam et al., 2001), or a specific finger and even an adjacent but not a non-adjacent finger (Kida et al., 2018). In contrast, SII responses from stimuli to the unattended sites have not been enhanced significantly from responses during a resting condition (Lam et al., 2001; Kida et al., 2018). The same has been shown with a somatosensory Go/NoGo paradigm, where SII responses were enhanced from a resting condition during the Go stimuli but not NoGo (Nakata et al., 2005).

4.4. Limitations and future prospects

This study has limitations. The TASK condition in our MEG recordings was not specific for increased attentional state and, hence not optimal for enhancing the SII responses. Silently counting the stimuli, as used in adults, is not applicable in young children. We also required a method where adequate compliance to the task could be verified; hence we used a motor response. SII responses to the little finger stimuli were not studied due to the coinciding squeezing-evoked motor response which could affect the nearby-located SII responses and, therefore, comparisons between Go- and NoGo-stimuli were unfeasible.

Our recording and analysis protocol was set up in an effort to be sensitive in detecting SII responses from the 6-year-old children's MEG data. However, despite using a fairly long and varying ISI (Hari et al., 1993; Hamada et al., 2003; Nevalainen et al., 2015) and employing mean locations and dipole orientations in the SII response modeling if individual modeling was not sufficient, not even all the control children in our study had clear SII responses present on both hemispheres. The activation patterns on SII areas to somatosensory stimuli vary among healthy adult subjects studied with functional MRI (Disbrow et al., 2000) and in MEG as well (Hari et al., 1993). While early SI responses are usually quite straightforward to model from MEG data, the longer-latency SII responses cannot always be reliably modeled from all adults either (Mima et al., 1998; Wegner et al., 2000; Lam et al., 2001; Hamada et al., 2003; Hadoush et al., 2010; Kida et al., 2018). In addition, a 6-year-old child's head is fairly small for an adult-sized MEG dewar helmet, and by recording MEG with the child's head in the midline may have resulted in smaller-amplitude responses more difficult to detect due to longer distance between the cortical sources and MEG sensors (Gaetz et al., 2008). While possibly not optimal for a good signal-to-noise ratio, recording MEG with the child's head in the midline in our study was first piloted with a few TB children showing SII responses on both hemispheres, and was chosen to reduce recording time to ensure compliance of our young subjects throughout the whole recording. At TEA, the even greater disparity between the size of the infant's head and the dewar helmet was solved by performing the recordings while the infants were lying on their side, but at the expense of being able to record only one hemisphere at a time.

SII responses are usually studied from MEG recordings but they can be reliably detected in optimal conditions in neonatal multichannel SEPs in electroencephalography as well (Nevalainen et al., 2015). It would be interesting to study the association between motor outcome and unilateral absence of an SII response in a larger infant cohort with multichannel electroencephalography which is more easily available in neonatal intensive care settings than MEG. Also, as SEPs to posterior tibial nerve, in contrast to median nerve, stimulation in preterm infants have come across as better predictors of cerebral palsy (Pierrat et al., 1997), it could be of value to study the SII responses to feet stimulation and their correlation with later motor outcome in EPB infants.

5. Conclusion

Unilateral absence of an SII response at TEA predicted poorer motor competence in EPB children approaching school-age. Clinical usability calls for further research in larger cohorts. Differences between the SII responses in EPB and TB children at age 6 years seem, however, more subtle than at TEA and they were, in this study, associated with differences in motor inhibition between these two groups of children. Whether these inhibition-related differences in the neurophysiological measures translate to problems in executive functioning remains an interesting prospect for future studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

MM and SA initiated the cohort study. PN, LL, EP and PL designed the MEG recordings, and AL, MM and PL designed the clinical outcome measures. PL, PN and EP collected and analyzed the MEG data with the help of JN. AL and PL performed the neuromotor examinations. PL performed the statistical analyses and drafted the manuscript. All authors contributed to the interpretation of the results, critically reviewed the manuscript and approved the final version to be published.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.04.005.

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